Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COMMENTARY

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Hydroxychloroquine for Coronavirus: The Urgent Need for a Moratorium on Prescriptions

Many issues concerning the prescription of chloroquine and hydroxychloroquine in the treatment and prevention of coronavirus 2019 (COVID-19) have been addressed in recent peer-reviewed publications in high-quality journals. Nonetheless, the widespread prescriptions by health care providers are 9 times greater than in the last several years.[1]

Perhaps this is due, in part, to the compassion of health care providers to do more good than harm in an ever increasingly alarming pandemic. Specifically, as of May 14, 2020, in the United States there have been over 1.3 million reported cases and over 84,000 deaths from COVID-19. Worldwide, the corresponding figures are over 4.3 million cases and almost 300,000 deaths. Thus, the United States accounts for over 30% of the cases and over 25% of the deaths while comprising only about 4.5% of the world's population. Of further alarm to health care providers and patients is that, at present, even without widespread rapid testing, the United States has already reported about 4 times the number of cases of any other country in the world, and even after adjusting for the population sizes, over 46 times the number of deaths of South Korea, whose first case was reported on the same day as that of the United States.[2]

It is also likely that widespread lay media reports, as well as statements by the highest-ranking US government officials, have also been a contributing factor. On April 4, 2020, the President of the United States publicly stated: "What do you have to lose? Take it, I really think they should take it." During the next 24 hours, the prescriptions of these drugs by health care providers skyrocketed to 46-fold above usual patterns.[1]

The continued widespread prescriptions by health care providers of these drugs for COVID-19 are, in turn, leading to nationwide shortages. Thus, patients with systemic lupus erythematosus and rheumatoid arthritis, for whom hydroxychloroquine has been an approved indication for decades, are unable to refill their prescriptions.[3]

In this Commentary, we review the totality of available evidence and conclude that there is an urgent need for a moratorium on the prescription of these drugs in the treatment and prevention of COVID-19.

When the totality of evidence is incomplete, it is appropriate for health care providers to remain uncertain.[4] Nonetheless, regulatory authorities are sometimes compelled to act on incomplete evidence. On March 28, 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for chloroquine and hydroxychloroquine for the treatment of COVID-19. By April 24, 2020, the FDA issued a Drug Safety Communication warning about potentially fatal prolongations of the QTc interval detectable on 12-lead electrocardiograms and risks of other serious cardiac arrhythmias. Thus, with chloroquine and hydroxychloroquine, as sometimes is the case, the accumulation of further reliable data later did not support the early regulatory action.

Advances in medical knowledge proceed on several fronts, optimally, simultaneously.[4] In basic research, hydroxychloroquine and chloroquine are structurally related and have similar mechanisms to inhibit the virus that causes COVID-19.[5] Despite their structural similarities, in vitro, hydroxychloroquine appears to be more effective. In addition, when used for lupus and rheumatoid arthritis, hydroxychloroquine has fewer side effects, fewer drug interactions, and is less toxic in overdose.

At present, the available evidence is restricted to 8 published studies: 5 on hydroxychloroquine alone, 2 on

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hydroxychloroquine plus azithromycin, and 1 on both in combination or alone. With respect to hypothesis testing, only large-scale randomized trials can reliably detect the most plausible small to moderate benefits.[4] Of 3 randomized trials, all were of inadequate sample size (225, 62, and 30 patients), and all tested hydroxychloroquine alone vs standard of care in China. One showed no significant difference in viral clearance at 28 days, the second, no difference in viral clearance at 7 days, and the third, improvements in fever, cough, and chest computed tomography findings.[6-8]

The chief concern about side effects is prolongation of the QTc interval on the 12-lead electrocardiogram. It has long been known that QTc prolongations of >40 ms or lesser increases in those with baseline values >500 ms are associated with fatal arrhythmias. As regards prescription of hydroxychloroquine, with or without azithromycin, for COVID-19, in a case series, the QTc interval was increased >40 ms in 18% and baseline QTc intervals were >500 ms in 11% and 20%, respectively. The US FDA Adverse Event Reporting System reported similar findings, but both lack a comparison group and can formulate, not test, hypotheses. In addition, azithromycin has little evidence for benefit when added to hydroxychloroquine, but also, independently prolongs the QTc interval.[9]

In summary, we recommend that health care providers restrict their prescriptions of hydroxychloroquine and chloroquine to compassionate use for patients with COVID-19 until the results of randomized trials that provide sufficient evidence. As regards risks, health care providers should be aware that the reassuring safety profile of hydroxychloroquine derives from decades of prescriptions for autoimmune diseases, which are of greater prevalence in younger and middle age women, whose risks of fatal outcomes due to prolongations of the QTc are reassuringly very low. In contrast, the risks for COVID-19 are so much higher because mortality rates are the highest in older patients and those with comorbidities, both of whom are predominantly men.

In conclusion, health care providers should always prioritize compassion *with* evolving science and safety data. In this context, we recommend a moratorium on the use of chloroquine or hydroxychloroquine, with or without azithromycin, to treat or prevent COVID-19, with the exceptions of obtaining the necessary evidence in randomized trials as well as compassionate use. If these drugs need to be prescribed for patients with COVID-19, baseline evaluations and serial monitoring are an absolute necessity.[9] We urge our competent and compassionate health care providers to adhere to the first words of the Hippocratic Oath of "primum non nocere."

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